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- anaemia during telaprevir-based triple therapy. *Liver Int* 2013. <http://dx.doi.org/10.1111/liv.12342>. [Epub ahead of print].
- [3] Hörl WH. Anaemia management and mortality risk in chronic kidney disease. *Nat Rev Nephrol* 2013;9:291–301.
- [4] Kunze A, Huwylar J, Camenisch G, Gutmann H. Interaction of the antiviral drug telaprevir with renal and hepatic drug transporters. *Biochem Pharmacol* 2012;84:1096–1102.
- [5] Karino Y, Ozeki I, Hige S, Kimura M, Arakawa T, Nakajima T, et al. Telaprevir impairs renal function and increases blood ribavirin concentration during telaprevir/pegylated interferon/ribavirin therapy for chronic hepatitis C. *J Viral Hepat* 2013. <http://dx.doi.org/10.1111/jvh.12162>. [Epub ahead of print].
- [6] Dumortier J, Guillaud O, Gagnieu MC, Janbon B, Juillard L, Morelon E, et al. Anti-viral triple therapy with telaprevir in haemodialysed HCV patients: is it feasible? *J Clin Virol* 2013;56:146–149.
- [7] Treitel M, Marbury T, Preston RA, Triantafyllou I, Feely W, O'Mara E, et al. Single-dose pharmacokinetics of boceprevir in subjects with impaired hepatic or renal function. *Clin Pharmacokinet* 2012;51:619–628.

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Evidence recommending antiviral therapy in hepatitis C

To the Editor:

Recently, Dr. Van der Meer and colleagues [1] discussed our systematic review of trials comparing interferon monotherapy to no therapy for retreating individuals infected with hepatitis C virus who had not achieved a sustained virological response (SVR) from previous antiviral therapy [2]. Our review made several observations: (1) retreatment with interferon monotherapy provided no relevant clinical benefit; (2) while there was a statistically significant reduction in non-fatal variceal bleeding, the number needed to treat (NNT) was so high (NNT = 67) that the treatment is economically unfeasible; (3) when only the low risk of bias trials were considered, interferon treatment increased all-cause mortality; (4) the recipients of interferon had more adverse events; and (5) the commonly used surrogate outcome of SVR occurred significantly more often in the treated group.

Since interferon treatment increased SVRs without improving clinical outcomes, the SVR was not a valid surrogate outcome in this scenario. As such, SVR cannot be universally considered as valid for purposes of clinical practice. We believe that, before it can be considered a trustworthy surrogate outcome in other scenarios, it must be validated in those scenarios, or at least in enough other scenarios that the single example of retreatment of interferon monotherapy could be considered to be an outlier.

Validation of a surrogate outcome is a two-step process [3]. First, there has to be a strong and consistent association between the surrogate outcome and the clinical one. However, association alone is not adequate to establish validation. It also has to be shown that improving the surrogate outcome also similarly improves the clinical one; in other words, a treatment-related difference between the study groups in the surrogate outcome should be associated with a proportionate treatment-related difference in the clinical outcome. This latter step can only be demonstrated in randomized clinical trial (RCTs). Most RCTs assessing

hepatitis C antiviral therapy do not provide clinical outcomes, presumably because these outcomes require years to pass before they begin to appear. Thus, there are limited data available to assess the validity of the SVR. Of note, several other Cochrane reviews also found scenarios in which an improved SVR did not translate into a meaningful beneficial clinical outcome. These included comparing interferon with or without ribavirin [4], using ribavirin alone [5], and employing interferon in treatment-naïve patients [6]. Dr. van der Meer and his colleagues cited two of these [4,6], but only noted that the improvement in SVR was accompanied by improvement in liver histology (another surrogate). Not mentioned by van der Meer *et al.*, adding ribavirin to interferon resulted in a minimal but statistically significant reduction in the combined endpoint of death and hepatic morbidity (0.28% reduced to 0.12%), but the NNT was 625 (compared to an NNT of 4 for achieving an SVR) [4].

Van der Meer *et al.* appeared to be most concerned with our statement that the presence of treatment harm and the failed validation of SVRs “should caution us to stop advocating antiviral interventions of any kind until we have evidence of clinical efficacy and cost-effectiveness” [2]. To support their argument that SVR is a good outcome to assess antiviral therapy, they cite a number of lines of evidence that demonstrate the association between SVR and good outcomes. We agree with them that the SVR is a good prognostic sign. However, the key issue is that the SVR has not been validated as a surrogate outcome. In other words, there are no RCTs that have shown that a treatment that increases the number of SVRs equates with improved clinical outcomes. Van der Meer *et al.* agree that this is the case.

We and van der Meer *et al.* also agree that most infected patients will not develop decompensated liver disease or hepatocellular carcinoma and that the prognostic factors identifying patients who are likely to achieve an SVR are also factors that

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would predict a good long-term outcome. If it is indeed true that the vast majority (perhaps even all) of individuals achieving SVRs were destined not to develop long-term complications of liver disease, it would follow that SVRs would be associated with non-progressive disease but that antiviral therapy may not provide overall benefit to the treated group.

To validate the SVR as a surrogate outcome, RCTs in the future should compare patients treated with regimens that result in larger percentages of SVRs (e.g., 90%) to untreated patients and employ clinical events as the primary outcome. If patients in previous RCTs did not subsequently receive additional treatment, we would encourage the authors of those trials to assess the long-term clinical outcomes retrospectively. As of this time, treatment advocates are supporting treatment that has no level 1 (well designed and executed RCTs) evidence for improved clinical outcomes, but is costly and toxic (including occasional mortal).

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

- [1] Van der Meer AJ, Wedemeyer H, Feld JJ, Nansen BE, Manns MP, Zeuzem S, et al. Is there sufficient evidence to recommend antiviral therapy in hepatitis C?. *J Hepatol* 2014;60:191–196.

- [2] Koretz RL, Pleguezuelo M, Arvaniti V, Barrera Baena P, Ciria R, Gurusamy KS, et al. Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C. *Cochrane Database Syst Rev* 2013;1:CD003617.
- [3] Bucher HC, Guyatt GH, Cook DJ, Holbrook A, McAlister FA. Users' guides to the medical literature XIX. Applying clinical trial results A. How to use an article measuring the effect of an intervention on surrogate end points. *JAMA* 1999;282:771–778.
- [4] Brok J, Gluud LL, Gluud C. Ribavirin plus interferon vs. interferon for chronic hepatitis C. *Cochrane Database Syst Rev* 2010;1:CD005445.
- [5] Brok J, Gluud LL, Gluud C. Ribavirin monotherapy for chronic hepatitis C. *Cochrane Database Syst Rev* 2009;4:CD005527.
- [6] Myers RP, Regimbeau C, Thevenot T, Leroy V, Mathurin P, Opolon P, et al. Interferon for interferon naive patients with chronic hepatitis C. *Cochrane Database Syst Rev* 2002;2:CD000370.

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Reply to: 'Evidence recommending antiviral therapy in hepatitis C'

To the Editor:

We thank Dr. Koretz and colleagues for responding to our appraisal of their Cochrane meta-analysis [1,2]. The discussion on the clinical benefits of antiviral therapy for chronic hepatitis C virus (HCV) infection is important because physicians should be aware of the strengths of current evidence as well as of the remaining uncertainties.

Koretz *et al.* again highlight and explain that sustained virological response (SVR) is not a validated surrogate marker as substantial proof from randomized placebo-controlled trials that antiviral therapy improves clinical outcome is lacking. As was clearly discussed in our recent review, this is correct. We also mentioned that the repeatedly found association between SVR and reduced cirrhosis-related morbidity and mortality might potentially be subject to residual confounding. Indeed, this possibility cannot be excluded in the performed cohort studies. However, in light of the extensive multivariate analyses in which SVR remained the most important factor associated with beneficial clinical outcome, we agree with others that it is hard to think of a confounder which would completely annihilate this association [3–5].

While recognizing that the possibility of residual confounding remains a scientific limitation, we have indeed challenged the

statement that no kind of antiviral therapy can currently be advocated. One of the key arguments by which Koretz *et al.* try to substantiate this statement is the increased mortality rate among interferon-treated patients as compared to controls, which was observed in their meta-analysis. However, it should be clearly mentioned that this was only found in the extended follow-up analyses of the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial, which almost solely drove their meta-analyses on SVR and mortality [6]. Unfortunately, in their response letter, Koretz *et al.* do not share their thoughts on the fact that all controls in the HALT-C study received a regular pegylated interferon (PegIFN) and ribavirin treatment course just prior to randomization. Consequently, this study compared long-term PegIFN therapy to short-term PegIFN therapy rather than to no treatment [7]. The design of the HALT-C trial thus prohibits extrapolation of the increased mortality rate as observed with long-term maintenance therapy to the regular PegIFN regimens. Therefore, this study should not have been included in the meta-analyses.

Our review did discuss that patients treated with interferon and ribavirin combination therapy had a beneficial clinical outcome as compared to patients treated with interferon monotherapy. In fact, as the improved clinical outcome is in line with the